

# P. Riederer, H. Reichmann, M. B. H. Youdim, M. Gerlach (eds.)

Parkinson's Disease and Related Disorders

Journal of Neural Transmission Supplement 70

### Prof. Dr. P. Riederer Klinik und Poliklinik für Psychiatrie und Psychotherapie Würzburg, Germany

Prof. Dr. H. Reichmann Universitätsklinikum der TU Dresden Dresden, Germany

Prof. Dr. M. B. H. Youdim Israel Institute of Technology Haifa, Israel

Prof. Dr. M. Gerlach Klinik und Poliklinik für Psychiatrie und Psychotherapie Würzburg, Germany

This work is subject to copyright.

All rights are reserved, whether the whole or part of the material is concerned, specifically those of translation, reprinting, re-use of illustrations, broadcasting, reproduction by photocopying machines or similar means, and storage in data banks.

Product Liability: The publisher can give no guarantee for the information contained in this book. This also refers to that on drug dosage and application thereof. In each individual case the respective user must check the accuracy of the information given by consulting other pharmaceutical literature. The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

#### © 2006 Springer-Verlag/Wien Printed in Austria

SpringerWienNewYork is part of Springer Science+Business Media springer.com

Typesetting: Thomson Press India Ltd., New Dehli Printing: Druckerei Theiss GmbH, 9431 St. Stefan im Lavanttal, Austria

Printed on acid-free and chlorine-free bleached paper

SPIN: 11516439

Library of Congress Control Number: 2006928439

With 75 Figures

ISSN 0303-6995 ISBN-10 3-211-28927-5 SpringerWienNewYork ISBN-13 978-3-211-28927-3 SpringerWienNewYork

Printed in Austria

#### **Preface**

It is our pleasure to present the Proceedings of the 16<sup>th</sup> International Congress on Parkinson's Disease (PD) and Related Disorders (16<sup>th</sup> ICPD) which took place in Berlin from June 5-9, 2005. This congress was the most successful congress ever with more than 3500 participants in the roaring German capital, consisting of an innovative program and with emphasis on bringing basic and clinical scientists together. Special attention has was paid in inviting young scientists. Therefore, the major aspect of scientific sessions was to identify young and up coming individuals in the field, with novel approaches to PD and novel models as a whole. The congress gave us the opportunity to present Germany and its capital after the burden of recent history in the new light of a reunified and peaceful country. We have succeeded in presenting the country as an important part of Europe and as a country of arts, architecture and renewal. The Congress attracted new friends from more than 75 countries worldwide. For this reason, we are most thankful to the World Federation of Neurology (WFN), Research Group on Parkinsonism and Related Disorders (RGPD), chaired by Professor Donald Calne for bringing this congress to Germany!

The Congress had many highlights with lectures covering all the major fields in PD and Related Disorders. The opening ceremony was highlighted by the inspiring presentation of Nobel Laureate Paul Greengard who lectured on dopamine-related signalling pathways in the brain, followed by the welcome addresses by Professor Riederer, President of the 16<sup>th</sup> ICPD, Professor Calne, President of the WFN-RGPD, Dr. Slewett, President emeritus of the National Parkinson Foundation, Miami, USA (NPF), Professor Kimura, President WFN, Professor Reichmann, President German Parkinson Society and Professor Einhäupl, Chairman of the Germany Science Council. The speeches were followed by a musical interlude of the "Sunday Night Orchestra" and the award ceremony of the WFN Research Committee on Parkinsonism and Related Disorders. The welcome reception presented typical German dishes and drinks.

In total the congress included 4 plenary lectures, 20 symposia, 6 hot topics, 4 video sessions, 1 workshop with

demonstration, 29 educational seminars, more than 600 posters which were presented throughout the congress, 44 guided poster tours, 4 poster symposia, and 14 satellite symposia.

There were many scientific highlights and this proceeding intends to give a representative overview of congress programme. In this preface we are only able to give a glimpse of the outstanding lectures and scientific events during the 5 days.

The congress started with a satellite symposium on the significance of neuromelanin in the human brain. This symposium was dedicated to Prof. Youdim on the occasion of his 65th birthday. These contributions are published separately in a Special Issue of the Journal of Neural Transmission. Professor Carlsson, 2000 Nobel Laureate, spent significant time at the congress site and was often seen discussing topics of mutual interest with congress participant's. There was an interesting new study presented by Professor Deuschl, Kiel, in which he demonstrates that deep brain stimulation results in even better outcome of motor function than regular medication. For this reason, he advocated earlier use of deep brain stimulation in PD. New medications were discussed in detail both in the plenary lectures and satellites and new drugs such as rasagiline, the new MAO-B-inhibitor and rotigotine, the new dermal patch, were discussed in detail. There were satellite meetings on apomorphine, COMT-inhibitors, levodopa, spheramine (a new promising cell therapy for the treatment of PD in the advanced stage), dopamine transporter scanning, dopamine agonists such as pramipexole, ropinirole and cabergoline, adenosine antagonists, restless legs, deep brain stimulation, botolinum toxine A, and the new lisuride dermal patch. All satellites were of highest quality and delivered valuable insights in present and new therapy of PD. Special lectures addressed the advent of gene therapy and stem cell therapy, although it is apparent that there is still a long way to go until this therapy cab be safe and affordable for many PD patients longing for disease modifying treatment.

VI Preface

Professors Schapira and Olanow gave an overview on the ever contradictory aspects of neuroprotection. While neuroprotection is generally accepted in animal models and cell culture, there is still discussion on whether SPECT-and PET-analyses and the delayed start design, as employed in the rasagiline study indicated neuroprotection in man. For neuroprotection to be successful earlier diagnosis of PD is mandatory. For this reason, groups from Amsterdam, Dresden, Tübingen and Würzburg are working on early diagnosis procedures such as olfactory tests, parenchymal sonography, REM sleep analyses, and biochemical markers.

There were lectures on treatment of PD and many on genetic abnormalities causing PD, mitochondrial abnormalities and other disturbances of cell function which lead to dopaminergic cell death.

The other major aspect of the scientific session was the field of basic neuroscience to illuminate our current understanding of how neurons die in sporadic and familial PD. This included symposia on development of midbrain dopaminergic neurons, the role of iron in neurodegeneration, and the progress on genetics and proteomics and the concept of developing novel multifunctional neuroprotective drugs for such a complex disease.

Twenty nine educational seminars covered the most important topics and problems in clinical science bringing theory to practice and treatment strategies.

The guided poster tours allowed exchange of scientific ideas and shed light on new findings in etiology, diagnosis and treatment of PD and related disorders.

A special highlight of the Congress was the Art Exhibition, demonstrating the creativity of our patients with movement disorders. This exhibition was organized by the German Parkinson's lay organisation as well as by the Austrian lay organisation. Professor Maurer, Frankfurt, presented Art from an Alzheimer's patient, the Carolus Horn Exhibition, which impressively demonstrated change in the way to paint during a dementive process.

Another highlight was the Medical Historical Exhibition which was organised by Dr. Ch. Riederer, Würzburg, which focused on the history of the treatment of PD and emphasized the Berlin contributions by H. Lewy, W. v. Humboldt, R. Hassler and others.

A special tribute was paid to Melvin Yahr who sadly passed away in early 2005 shortly before this Congress. He was greatly missed.

Due to generous educational grants from the industry the organizers were able to honour outstanding scientists and clinicians, Toshiharu Nagatsu, Yoshikuni Mizuno, Japan (Award of the WFN Research Group on Parkinsonism and Related Disorders), Saskia Biskup, Germany and Andrew B. Singleton, USA (16th ICPD Junior Research Award), Jonathan Brodie, Canada and Alan Crossman, UK (Merck KGaA Dyskinesia Research Award). GE Healthcare sponsored the 16th ICPD Senior Researcher Award given to Silvia Mandel, Israel and Vincenzo Bonifati, The Netherlands. Both companies gave educational grants for the 12 Poster Prizes while the Melvin Yahr Foundation sponsored 26 Fellowships. In addition the congress made it possible to bring numerous young scientists to the congress by giving them financial support for travelling and accommodation.

The Senator Dr. Franz Burda Award presented by Helmut Lechner, Austria, and Franz Gerstenbrand, was given to Laszlo Vecsei, Hungary and Tino Battistin, Italy.

We thank all the participants who gave us their creative input to organize a World Congress on PD (as indicated in the First Announcement) which fulfilled the criteria of excellence and made the congress so successful. This was YOUR congress and which many of you influenced by letting us know your wishes and expectations. New concepts, formats and innovations, the active and constructive cooperation by the participating industry and the lay organisations made all this possible. This can measured by the numerous complimentary letters and emails we have received since then and we hope it sets the standards for future meetings! By doing all this we tried to come close to our milestone "Present and Future Perspectives of Parkinson's Syndrome".

Our special thanks go to CPO Hanser Congress Organisation, the programme committee and the WFN Research Group which all worked so hard to make this Congress so successful.

Finally the congress proceedings are published and we thank all those who contributed to this volume. Special thanks go to Springer Verlag, Vienna, New York for their efficient and splendid ability in being able to publish the proceeding so rapidly.

Peter Franz Riederer, Heinz Reichmann, Moussa Youdim, Manfred Gerlach Würzburg, Dresden, Haifa, spring 2006

## Contents

| <b>Powell, C.:</b> Melvin Yahr (1917–2004). An appreciation                       | 1<br>5    |
|---|-----------|
| 1. Pathology  |           |
| Hornykiewicz, O.: The discovery of dopamine deficiency                            | 0         |
| in the parkinsonian brain   | 9         |
| Heimer, G., Rivlin, M., Israel, Z., Bergman, H.: Synchronizing activity           | 17        |
| of basal ganglia and pathophysiology of Parkinson's disease                       | 17        |
| in Parkinson's disease  | 21        |
| Brown, P.: Bad oscillations in Parkinson's disease                                | 27        |
| McKeown, M. J., Palmer, S. J., Au, WL., McCaig, R. G.,                            | 21        |
| Saab, R., Abu-Gharbieh, R.: Cortical muscle coupling in Parkinson's disease       |           |
| (PD) bradykinesia   | 31        |
| Burke, R. E.: GDNF as a candidate striatal target-derived neurotrophic            |           |
| factor for the development of substantia nigra dopamine neurons                   | 41        |
| Gherbassi, D., Simon, H. H.: The engrailed transcription factors                  |           |
| and the mesencephalic dopaminergic neurons  | 47        |
| Smits, S. M., Smidt, M. P.: The role of Pitx3 in survival of midbrain             |           |
| dopaminergic neurons  | 57        |
| Ryu, S., Holzschuh, J., Mahler, J., Driever, W.: Genetic analysis of dopaminergic |           |
| system development in zebrafish   | 61        |
| Deutch, A. Y.: Striatal plasticity in parkinsonism: dystrophic changes            | <b>67</b> |
| in medium spiny neurons and progression in Parkinson's disease                    | 67        |
| Fuxe, K., Manger, P., Genedani, S., Agnati, L.: The nigrostriatal DA pathway      | 71        |
| and Parkinson's disease   | 71        |
| and neuronal degeneration in basal ganglia  | 85        |
| Braak, H., Müller, C. M., Rüb, U., Ackermann, H., Bratzke, H.,                    | 65        |
| de Vos, R. A. I., Del Tredici, K.: Pathology associated with sporadic             |           |
| Parkinson's disease – where does it end?  | 89        |
| Halliday, G. M., Del Tredici, K., Braak, H.: Critical appraisal of brain          | 0)        |
| pathology staging related to presymptomatic and symptomatic cases                 |           |
| of sporadic Parkinson's disease   | 99        |
| Giorgi, F. S., Bandettini di Poggio, A., Battaglia, G., Pellegrini, A.,           |           |
| Murri, L., Ruggieri, S., Paparelli, A., Fornai, F.: A short overview              |           |
| on the role of $\alpha$ -synuclein and proteasome in experimental models          |           |
|   | 105       |
| Gispert-Sanchez, S., Auburger, G.: The role of protein aggregates                 |           |
| in neuronal pathology: guilty, innocent, or just trying to help?                  | 111       |

VIII Contents

| 2. Iron and neuromelanin   |
|--|
| Double, K. L., Halliday, G. M.: New face of neuromelanin   |
| dopaminergic SH-SY5Y cells   |
| of parkinsonian patients   |
| 3. Genetics  |
| Chade, A. R., Kasten, M., Tanner, C. M.: Nongenetic causes   |
| of Parkinson's disease   |
| caused by the consumption of Annonacae?  |
| <b>Mellick, G. D.:</b> CYP450, genetics and Parkinson's disease: gene×environment interactions hold the key  |
| Ravindranath, V., Kommaddi, R. P., Pai, H. V.: Unique cytochromes  |
| P450 in human brain: implication in disease pathogenesis   |
| from MPTP toxicity   |
| Miksys, S., Tyndale, R. F.: Nicotine induces brain CYP enzymes: relevance to Parkinson's disease   |
| Riess, O., Krüger, R., Hochstrasser, H., Soehn, A. S., Nuber, S., Franck, T., Berg, D.: Genetic causes of Parkinson's disease:                         |
| extending the pathway  |
| Tomiyama, H., Li, Y.: Progress in familial Parkinson's disease   |
| in Park2 and regulation of parkin protein by other proteins  |
| <b>Heutink, P.:</b> PINK-1 and DJ-1 – new genes for autosomal recessive Parkinson's disease  |
| Whaley, N. R., Uitti, R. J., Dickson, D. W., Farrer, M. J., Wszolek, Z. K.: Clinical and pathologic features of families with <i>LRRK2</i> -associated |
| Parkinson's disease  |
|  |
| 4. Imaging   |
| Lu, CS., Wu Chou, YH., Weng, YH., Chen, RS.: Genetic and DAT imaging studies of familial parkinsonism in a Taiwanese cohort                            |
| Lok Au, W., Adams, J. R., Troiano, A., Stoessl, A. J.:   |
| Neuroimaging in Parkinson's disease  |
| <b>Berg, D.:</b> Transcranial sonography in the early and differential diagnosis   |

Contents IX

| 5. Models  |
|--|
| Hirsch, E. C.: How to judge animal models of Parkinson's disease in terms  |
| of neuroprotection   |
| in Parkinson's disease research  |
| of Parkinsonism – the five years inspection  |
| <b>Schmidt, W. J., Alam, M.:</b> Controversies on new animal models of Parkinson's disease Pro and Con: the rotenone model   |
| of Parkinson's disease (PD)  |
| 6-hydroxydopamine lesion of dopaminergic innervation of striatum   |
| and other neurodegenerative disorders: preclinical and clinical studies  |
| 6. Clinical approaches   |
| Goetz, C. G.: What's new? Clinical progression and staging of Parkinson's disease 305 Wolters, E. Ch., Braak, H.: Parkinson's disease: premotor  |
| clinico-pathological correlations  |
| along the olfactory trac(t)  |
| in Parkinson's disease; maintaining independent mobility   |
| Bodis-Wollner, I., Jo, MY.: Getting around and communicating with the environment: visual cognition and language in Parkinson's disease  |
| Comella, C. L.: Sleep disturbances and excessive daytime sleepiness in Parkinson disease: an overview  |
| <b>Arnulf, I.:</b> Sleep and wakefulness disturbances in Parkinson's disease   |
| 7. Neuroinflammation   |
| <b>Burn, D. J.:</b> Parkinson's disease dementia: what's in a Lewy body?   |
| degeneration of dopaminergic neurons: neuroprotective effect of Interleukin 10 367 <b>Sawada, M., Imamura, K., Nagatsu, T.:</b> Role of cytokines in inflammatory  |
| process in Parkinson's disease   |
| 8. Neurosurgery  |
| Benabid, A. L., Chabardès, S., Seigneuret, E., Fraix, V., Krack, P., Pollak, P., Xia, R., Wallace, B., Sauter, F.: Surgical therapy for Parkinson's disease  |
| <b>Hamani, C., Neimat, J., Lozano, A. M.:</b> Deep brain stimulation for the treatment of Parkinson's disease  |
| Stefani, A., Fedele, E., Galati, S., Raiteri, M., Pepicelli, O., Brusa, L., Pierantozzi, M., Peppe, A., Pisani, A., Gattoni, G., Hainsworth, A. H., Bernardi, G., Stanzione, P., Mazzone, P.: Deep brain stimulation |
| in Parkinson's disease patients: biochemical evidence  |

X Contents

| Agid, Y., Schüpbach, M., Gargiulo, M., Mallet, L., Houeto, J. L., Behar, C., Maltête, D., Mesnage, V., Welter, M. L.: Neurosurgery in Parkinson's disease: the doctor is happy, the patient less so?   |
|--|
| 9. L-Dopa  |
| de la Fuente-Fernández, R., Lidstone, S., Stoessl, A. J.: Placebo effect and dopamine release  |
| 10. Neuroprotection  |
| Uitti, R. J., Wszolek, Z. K.: Concerning neuroprotective therapy for Parkinson's disease   |
| <b>Zigmond, M. J.:</b> Triggering endogenous neuroprotective mechanisms in Parkinson's disease: studies with a cellular model  |
| multifunctional drug for the treatment of dementia co-morbid with depression   |
| Weinreb, O., Amit, T., Bar-Am, O., Sagi, Y., Mandel, S., Youdim, M. B. H.:  Involvement of multiple survival signal transduction pathways in the neuroprotective, neurorescue and APP processing activity of rasagiline and its propargyl moiety |
| 11. Other treatment strategies   |
| Schulz, J. B.: Anti-apoptotic gene therapy in Parkinson's disease  |
| 12. Dystonia   |
| Hallett, M.: Pathophysiology of dystonia   |
| Index  |

**Listed in Current Contents/Life Sciences**